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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,584	08/25/2003	Arthur M. Krieg	C1039.70084US00	5262
23628 7590 06/14/2007 WOLF GREENFIELD & SACKS, P.C. 600 ATLANTIC AVENUE BOSTON, MA 02210-2206			EXAMINER MARVICH, MARIA	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<p align="center"><b>Office Action Summary</b></p>	<p><b>Application No.</b></p> <p align="center">10/649,584</p>	<p><b>Applicant(s)</b></p> <p align="center">KRIEG ET AL.</p>	
	<p><b>Examiner</b></p> <p align="center">Maria B. Marvich, PhD</p>	<p><b>Art Unit</b></p> <p align="center">1633</p>	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 March 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and, therefore, this action is final.

#### *Claim Rejections - 35 USC § 112, first paragraph :*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering an unmethylated CpG nucleic acid wherein when the CpG nucleic acid is an adjuvant nucleic acid, it is administered in the presence of a vaccine to a subject infected with HIV to induce B cells, natural killer cells and IL-6, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 10/18/06 and restated below.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

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App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

**1) Nature of invention.** The instant claims are drawn to a method for treating a subject by administration of CpG nucleic acid to a subject infected with HIV to treat the infection.

**2) Scope of the invention.** The scope of the invention is extremely broad in that the claims are drawn to treatment of any subject infected with any HIV virus by administration of any CpG nucleic acid. While, dependent claim 2 limits the nucleic acid to one that does not include a palindrome and claim 3 to an adjuvant type CpG nucleic acid and claim 4 to an IFN- $\alpha$ -inducing CpG, the nature of the CpG nucleic acid is still very broad. The broad nature of the CpG nucleic acid that encompasses methylated as well as unmethylated nucleic acids coupled with the highly unpredictable nature of treating anyone infected with HIV renders the claimed invention highly unpredictable.

**3) Number of working examples and guidance.** The specification teaches an immunostimulatory CpG containing oligonucleotide, which includes at least one, unmethylated CpG dinucleotides. An unmethylated CpG dinucleotides is disclosed as one that contains an unmethylated cytosine in a cytosine-guanine dinucleotides. The specification teaches that the CpG dinucleotides can be adjuvant or IFN- $\alpha$  inducing CpG nucleic acid. The specification teaches that the oligonucleotide is administered with a vaccine as an adjuvant to boost a subject's immune system to effect a better response to the vaccine. The specification appears to suggest that an adjuvant CpG nucleic acid has requirements that distinguish it from an immunostimulatory nucleic acid. For example an immunostimulatory nucleic acid is presented by the formula of 5'-X<sub>1</sub>X<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub>-3' while an adjuvant type has one of two base sequences in

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SEQ ID NO:27 and 28. These are 5'-TCN<sub>1</sub>TN<sub>2</sub> X<sub>1</sub>X<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub>-3' and 5'-TCN<sub>1</sub>T X<sub>1</sub>X<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub>-3'. Specifically, SEQ ID NO:27-34 are presented as models for sequences that function as adjuvant CpG molecules. However, the disclosure also teaches that SEQ ID NO:29 and 35-72 function as immunostimulatory molecules. The specification continues that IFN- $\alpha$ -inducing CpG nucleic acid comprise SEQ ID NO:73, 5'-Y<sub>1</sub>N<sub>1</sub>X<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub> N<sub>2</sub> Y<sub>2</sub>-3' as the model sequences but also teach that SEQ ID NO:30 functions specifically as one such molecule. It is noted that SEQ ID NO:s 28-74 have been presented in parent application 09/931583, filed 8/16/01. The as filed instant specification and parent applications exemplify function of SEQ ID NO:s 2, 5, 6, 7, 8, 11, 13-15, 18, 21, 26 and TCAACGTT by administration of these sequences to uninfected mice resulting in enhanced IgM production, natural killer cells and IL-6. The specification provides no working examples directed toward methods of treating HIV or any guidance as to the response of the subject to CpG nucleic acids that would lead one to believe that the nucleic acids can treat HIV infection.

**4) State of the art.** Current guidelines have established that the goal in medical management of HIV infection and AIDS is maximal suppression of HIV replication. To do so, triple therapy is recommended starting with protease inhibitor. By inhibiting viral load at initial infection emergence of drug resistant strains can be avoided (see e.g. De Cock, page 1, ¶ 2-3).

**5) Unpredictability of the art.** The claims are directed to a method for treating an HIV infected patient therapeutically. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750

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F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b)). In the instant case, the claims are extremely broad in reciting treatment of a subject with HIV infection. The response to HIV infection is multifaceted and complex often resulting in AIDS. The specification describes use of DNA structures to activate lymphocytes such as B-cell proliferation and immunoglobulin secretion. As well, the specification exemplifies this embodiment by administration of CpG oligonucleotide to uninfected mice resulting in enhanced IgM production, natural killer cells and IL-6. Hence, the specification appears to be drawn to a definition of treatment limited to an enhancement of the immune system. The as-filed specification proposes use of three types of CpG molecules, immunostimulatory, adjuvant and IFN- $\alpha$  inducing molecules. It is not clear that these molecules cannot function in all three categories. With regard to adjuvant nucleic acids, the specification teaches that these nucleic acids would mediate response that would function to boost a subject's response to a vaccine and provide several examples of such sequences and assay the immunostimulating activity of these molecules. However, the specification does not disclose the type of vaccine to be used with the nucleic acids nor does it demonstrate use of the nucleic acid as an adjuvant. Applicants have attempted to define an adjuvant type molecule in by introduction of SEQ ID NO:s 27-72 in 09/931,853. With regard to IFN- $\alpha$  inducing nucleic acids, applicants propose two sequences again introduction in parent application 09/931,853 upon which the IFN- $\alpha$  inducing nucleic acids are based. However, neither of the types of sequences is used to produce an IFN- $\alpha$  induction. Rather, the specification demonstrates the immunostimulatory function of these molecules in uninfected mice. Hence, the application does not provide sufficient guidance and/or evidence demonstrating a reasonable extrapolation from

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the disclosure to use of adjuvant CpG, IFN- $\alpha$  inducing CpG or any CpG molecule in any subject infected with any HIV to treat HIV infection given the highly unpredictable nature of the recited subject matter.

First, as summarized by Cohen and Fauci (1998), HIV therapy even many years post-filing is still hindered by inadequate treatments. This article also highlights those problems that have confounded treatment to date- HIV reside latent in cells in immunoprivileged sites, causes immunosuppression, destroys immune cells and continually mutates resulting in different strains in parts of the world. Hence treating HIV means that vaccines developed against one strain does not ensure treatment of other strains. As well, infected persons can harbor multiple forms of the virus. More specifically as it relates to the instant invention, Cohen and Fauci teach that treatment is affected by the lack of a vaccine. "Development of a safe and effective vaccine for HIV infection remains the "holy grail" of AIDS research". "The development of a safe and effective vaccine continues to encounter a host of sobering challenges, including geographic variability of HIV subtypes, and the lack of correlates of protective immunity in HIV infection." (page 88, col 1, ¶ 3). However, the instant claims recite use of CpG as an adjuvant. As neither the specification nor the state of the art demonstrate a potential vaccine that is effective, CpG cannot act as an adjuvant. While the claims are drawn to any CpG nucleic acid, the specification teaches the CpG molecule must be unmethylated. This is due to the effect the immune induction by molecules typically not present in mammalian cells. Bacterial molecules lacking methylation are not potent immune inducers than methylated molecules. But it is apparent that even considering the state of the art of CpG therapy using even unmethylated CpG nucleotides, the art is highly unpredictable. It has been discovered that there is species selection when considering

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the optimal motif for immunostimulatory effects differs between species. Specifically, Agrawal (2002) teaches, “The DNA sequences containing an unmethylated CpG dinucleotides flanked by two purine bases on the 3’ side, such as GACGTT, were found to activate the mouse immune system efficiently. However, the human immune cells responded poorly to this hexameric motif, suggesting that the sequences required for CpG-related immune stimulation varies from species to species”. (bridging ¶page 114-115). Hence, any motif demonstrated to be significant in mice models does not project the success of that motif for humans. The optimal motif listed in the specification is said to be TGACGTT/C. This matches that found to be optimal in mice.

Whereas for humans, this sequence is GTCGTT or TTCGTT. The success of any other sequence is unpredictable. Species specificity is thought to be due to the species specificity of the toll ligand receptor. Mackichan (2005) teaches that “One complication to development of novel TLR ligands for use in human vaccines is the species-specificity of TLR expression, ligand recognition, and DC subsets. Mice can make a robust immune response that include CTL in response to vaccination with TLR ligands, such as CpG oligonucleotides and protein antigen, but the CD8+ DC subset responsible may not be present in primates”. (page 5, col 1, ¶ 2) At this time, it was apparent that CpG molecules that function as adjuvant had yet to be discovered.

Secondly, with respect to the state of the art, methods of treatment utilizing CpG nucleic acids were clearly unpredictable for humans. Schwartz et al have found that CpG motifs lead to inflammation in the lungs and contribute to disease progression and morbidity in some forms of lung disease (see e.g. page 68, col 1, ¶ 2). Oehen et al (2000) found that DNA vaccination with CpG was not able to produce CTL protective responsive against infection of a peripheral organ,



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which is the benchmark of treatment. As well, DNA vaccination was very short-lived and does not induce effector or memory CTL.

Given the lack of guidance in the specification, the large and diverse group of molecules for treatments recited and the highly unpredictable nature of the art, it is concluded that a person of skill in the art would have had to conduct undue experimentation in order to practice the claimed invention.

**6) Amount of Experimentation Required.** The invention recites use of a broad group of molecules to treat any subject infected with any HIV. Given the unpredictability of the art, the poorly developed state of the art with regard to CpG therapies, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

### *Response to Argument*

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 4-9 of the amendment filed 3/28/07. Applicants' arguments filed 3/28/07 have been fully considered but they are not persuasive. Applicants argue that adjuvant/immunostimulatory CpG molecules are not mutually exclusive and specifically the formula for immunostimulatory CpGs has been provided and this formula encompasses both adjuvant and IFN- $\alpha$  inducing CpG molecules. It is noted that applicants have given the common definition to adjuvant and immunostimulatory. However, the basis of the unpredictability as to identifying adjuvant versus immunostimulatory CpG molecules has less to do with the functional definition of the terms than the ability to structurally identify each one. It is clear the purpose of either would be distinct and

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yet applicants have not provided the structural requirements of either and so it is not clear how to distinguish between the two types of structures and how to know whether one was using an adjuvant type CpG or an immunostimulatory CpG. Applicants do not teach one of skill in the art what an adjuvant CpG versus immunostimulatory versus IFN- $\alpha$  inducing CpG molecule looks like and the claims require that such a selection be made.

Applicants argue that working examples are not required and that treatment does not mean cure or eradication of HIV. Though not controlling, the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. *Ex parte Sudilovsky*, 21 USPQ2d 1702, 1705 (BPAI 1991); *In re Novak*, 134 USPA 335 (CCPA 1962); *In re Fouche*, 169 USPQ 429 (CCPA 1971). In the instant case, the underdeveloped state of the art of treatment of HIV infection has been demonstrated above. Hence, the lack of working examples is a factor in considering whether adjuvants of HIV treatment would be effective. Whether an invention is enabled or not does not break down to the question of whether individual components or steps of the invention have the potential of operating as intended but rather if the invention as a whole will function as recited. The instant disclosure does not provide adequate guidance for treatment of HIV. The administration of unmethylated CpG nucleic acids stimulate B cells, induce IL-6 production and activate NK cells, which does not meet the standards of treatment even as defined in the specification where applicants argue treatment comprises a reduction in viral load following

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administration of the active agents. To this applicants state that unmethylated CpG an contribute to overall viral reduction. However, and as the references set forth the ability to define that active agent that is added to which CpG will act as an adjacent is highly unpredictable.

The instant invention has been assessed completely as it relates to the prior art in light of the guidance provided in the specification. In response to the art, applicants argue that the wrong standard has been applied and they need not demonstrate safety nor clinical trials. As well, applicants argue that it is common to deal with species differences in treating disease. Human trials have not been requested nor are safety standards deemed as required to overcome a charge of undue experimentation. Rather, the references have been provided to illustrate the underdeveloped state of treatment of HIV infection. These references also teach that in the field of CpG therapy, the success of any other sequence is unpredictable. The optimal motif listed in the specification is said to be TGACGTT/C. This matches that found to be optimal in mice. Whereas for humans, this sequence is GTCGTT or TTCGTT. Any motif demonstrated to be significant in mice models does not project the success of that motif for humans. Given the unpredictability of the art, the poorly developed state of the art with regard to CpG therapies, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

### ***Double Patenting***

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

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The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 2 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37-56 of copending Application No. 10/788,191.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims as being unpatentable over claims 37-56 of copending Application No. 10/788,191. That is, the cited claims of U.S. Application No. 10/788,191 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, both applications recite a method of treating HIV using a CpG nucleic acid wherein the nucleic acid is not a palindrome.

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Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the U.S. Application No. 10/788,191, then two different assignees would hold a patent to the claimed invention of U.S. Application No. 10/788,191, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 37, 45, 46, 50, 56-58 of copending Application No. 11/067,516.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims as being unpatentable over claims 37, 45, 46, 50, 56-58 of copending Application No. 11/067,516. That is, the cited claims of U.S. Application No. 11/067,516 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, both applications recite a method of treating HIV using CpG nucleic acids.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the U.S. Application No. 11/067,516, then two

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different assignees would hold a patent to the claimed invention of U.S. Application No. 11/067,516, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Response to Argument***

It is acknowledged that applicants' will address the provisional obviousness double patenting rejections upon indication of allowable subject matter. However, until the recited claims are patented or a terminal disclaimer is filed, the claims remain rejected.

### ***Conclusion***

No Claims allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD  
Examiner  
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